

A Normal Baby Girl Born to a Chinese Woman with Classical Congenital Adrenal Hyperplasia

KM *BELARAMANI*, LM *WONG*, NS *KWONG*

Abstract Women having congenital adrenal hyperplasia (CAH) owing to 21-hydroxylase deficiency, especially those with salt-losing type, have decreased fertility rates. With advances in genital reconstruction, reproductive medicine and optimisation of antenatal care for this group of patients, more documented successful pregnancies have been reported. We report a Chinese woman with classical salt-losing type of CAH who has successfully delivered a normal baby girl.

Key words Adrenal hyperplasia; Congenital; Pregnancy

Introduction

Congenital adrenal hyperplasia (CAH) is a rare disease. Newborn screening programs relying on 17-hydroxyprogesterone (17-OHP) measurements using a filter paper blood spot sample suggests that CAH owing to 21-hydroxylase deficiency occurs with an incidence of 1:15,000 in Canada and the United States combined.¹ Lee et al reported the incidence to be even lower (1:28000) in the Chinese population.² Salt-losing type of CAH accounts for two thirds of the cases, the remaining cases are non-salt-losing type.

Women having CAH have decreased fertility. In 1987, Mulaikal et al³ reported no live births in 40 women with classical salt-losing CAH. In 1995, Kuhnle et al⁴ reported

2 live births in 20 women and more recently, in 2004, Hoepffner et al⁵ reported 9 births in 6 women. The improved fertility rate with time is attributed to advances in genital reconstruction, reproductive medicine and optimisation of perinatal care for this group of patients. In this report, we describe a Chinese Woman with salt-losing CAH who has successfully delivered a normal baby girl.

Case Report

A 27-year-old woman with the salt-losing type of CAH conceived spontaneously and was followed up during pregnancy. She was first seen by us at the age of 10 years old when she was referred to us by another hospital for geographical reasons. The patient herself was born to non-consanguineous parents at 38 weeks and 3 days of gestation by Caesarean section with a birth weight of 3.1 kilograms. Masculinized external genitalia was detected at birth: enlarged phallus, hyperpigmented genitalia and a single urogenital opening. Chromosomal study confirmed 46XX. However, neither 17-OHP nor genetic study results were mentioned as the initial workup panel in the referral letter. She had salt-losing crisis on Day 9 and was started on cortisone and fludrocortisone therapy. Reconstruction of the external genitalia was performed at 2 years of age.

Department of Paediatrics and Adolescent Medicine, Tuen Mun Hospital, Tsing Chung Koon Road, Tuen Mun, New Territories, Hong Kong, China

KM *BELARAMANI* (尹綺琪) *MBBS, MRCPCH*
LM *WONG* (黃立明) *MBBS, FHKAM(Paed)*
NS *KWONG* (龔毅山) *MBBS(HK), MRCP(UK), FHKAM(Paed)*

Correspondence to: Dr KM *BELARAMANI*

Received August 27, 2009

She attended medical follow-up regularly since diagnosis. Her height was along the third to tenth percentile of the population height curve which was the same as the percentile for her mid parental height (151 cm). Her thelarche, pubarche and menarche were at 11.5 years old, 13.5 years old and 14.2 years old respectively. Menstruation was regular all along. Regular serum 17-OHP showed fluctuating levels especially when the patient had short periods of poor drug compliance. However she had no signs of virilisation i.e. excessive acne, deepening of voice, hirsutism etc. Besides, she had no further episode of acute adrenal insufficiency and her adult height was 151.8 cm which was within the target range of her mid-parental height.

Revision of the vaginal reconstruction was done at 24 years of age. She got married soon after the operation. Clinical genetic service was consulted but no blood test for the male partner was done. No problem was encountered in sexual intercourse and the couple used condom for contraception. At 26 years of age, they planned for pregnancy and stopped contraception. The patient conceived spontaneously within 2 months. Serial body weights, growth in fundal size and blood pressure readings were satisfactory and no specific problems were encountered during the antenatal period. The dosage of fludrocortisone acetate was 100 micrograms daily and hydrocortisone was 30 mg daily in divided doses prior to the pregnancy. Routine testosterone level before pregnancy was 1.91 nmol/L. At 16 weeks of gestation, testosterone level was 6.61 nmol/L (reference range for second trimester 2.7-6.3 nmol/L) and 17-OHP was 41.1 nmol/L (reference range for second trimester 7.7-30.1 nmol/L). Thus hydrocortisone dosage was increased to 40 mg daily, whereas the fludrocortisone dose was kept unchanged. At 25 weeks gestation, testosterone level was 5.31 nmol/L (reference range for third trimester 2-6 nmol/L) and 17-OHP was 19.6 nmol/L (reference range for third trimester 24.5-84 nmol/L). The reference ranges of testosterone and 17-OHP were adapted from Quest Diagnostics, Nichols Institute.⁶

At full term, she underwent an uneventful elective Caesarean section with peri-operative stress dose of hydrocortisone cover. The indication for Caesarean section was previous vaginal surgery. A healthy baby girl with a birth weight of 2.86 Kilograms was delivered. The baby had normal genitalia and her serum 17-OHP level was 2 nmol/L on Day 3, making the diagnosis of CAH unlikely.

Our patient's hydrocortisone dose was returned to 30 mg daily 6 weeks after delivery.

Discussion

CAH owing to 21-hydroxylase deficiency leads to reduced or absent cortisol production. Decreased cortisol production then stimulates adreno-cortico-trophic hormone (ACTH) secretion which in turn causes adrenal hyperplasia. Increased ACTH production also leads to accumulation of high concentrations of steroid metabolites before the enzymatic block. In the absence of cortisol, the secretion of gonadotropins from the pituitary is impaired and so is the function of hypothalamic pituitary-adrenal axis. All of the above is assumed to disturb pubertal development and make pregnancy difficult to achieve by a mechanism not completely understood to date.

In the literature, there are many reports regarding pregnancies in patients with simple virilizing CAH and those with late onset CAH, but fertility rates of patients with salt-losing CAH are much lower. Several factors have been implicated regarding the cause for reduced fertility rate in women with CAH. One factor is the suboptimal repair of the masculinized external genitalia resulting in inadequate vaginal introitus, leading to unsatisfactory sexual intercourse, and reduced sexual activity and thus reduced fertility.³ Another contributing factor may be inadequate treatment which can result in poor androgen suppression and elevated androgen levels leads to anovulation.^{1,5} Moreover, Hoepffner et al reported that even with optimal treatment, one third of patients with CAH do not have sexual interest or fantasies.⁵ This, in turn, results in lack of heterosexual activity and thus reduced fertility. An increased level of homosexuality³ and low maternalism⁷ has also been implied in CAH patients. Therefore an impaired development of sexual centre has been implicated in the reduced fertility rates seen in CAH patients.

Progesterone levels are noted to be abnormally elevated in the follicular phase of the cycle in patients with CAH.⁵ The underlying physiology of this phenomenon is unknown. This hormonal disturbance is associated with anovulatory cycles and failure to implant to the thin endometrium.⁸ Progesterone levels remain elevated even after adequate suppression of 17-OHP.⁸ Ogilvie et al⁷ reported two cases who underwent bilateral adrenalectomy and found that their progesterone levels dropped after the procedure. After

suffering from infertility for years, both these women conceived spontaneously. In our patient, pregnancy was achieved spontaneously. Lo et al⁶ also reported 3 out of 4 patients in which conception was spontaneous.

Once pregnancy is achieved, new issues regarding management during pregnancy arise. There is no international guideline for the management of these patients during pregnancy and delivery. The management during pregnancy becomes particularly important if the fetus in question is female, like in our case, because differentiation of external genitalia into male type is induced by testosterone/dihydrotestosterone in the first trimester. Thus, varying degree of masculinization of the female fetus could occur if maternal androgen levels are high during that period. There has been one report of an androgen induced masculinization of external genitalia of a baby girl born to a mother with simple virilizing form of CAH who ceased steroid treatment before conception.⁷

However, not all fetuses develop virilization in-utero despite exposure to high androgen levels. Lo et al⁶ reported a case in which the female fetus was unaffected by a total testosterone level of 13.5 nmol/L and a free testosterone level of 1 nmol/L. Protection of the female fetus has also been observed in cases of maternal hyperandrogenism owing to polycystic ovarian syndrome.⁹ Several protective mechanisms have been postulated. Placental aromatization of maternal testosterone and androstenedione to estradiol and estrone is one key postulation.¹⁰ Aromatase concentration and total aromatase activity in human placenta is increased during pregnancy and this may confer greater fetal protection against virilization. This phenomenon's importance is well illustrated by Shozu et al¹⁰ who reported masculinization of the external genitalia in a baby girl with placental aromatase deficiency.

Predicting the sensitivity of the fetus to androgen exposure in-utero is difficult and thus the aim of management during pregnancy should be to suppress maternal androgens adequately with the least amount of glucocorticoid so as to avoid complications. To achieve this, Ogilvie et al⁷ suggested two strategies. Firstly, to maintain glucocorticoid replacement at pre-pregnancy doses and increasing doses of hydrocortisone and mineralocorticoid as indicated by maternal symptoms alone. The second is to monitor testosterone and 17-OHP regularly during pregnancy and aim to suppress these markers to the high normal pregnancy range. Monitoring maternal symptoms alone is very subjective and thus in our case, the second

strategy was adopted. The glucocorticoid dose was increased according to the testosterone and 17-OHP levels. Our patient had no complications during pregnancy and she underwent a smooth elective Caesarean section. For the four cases reported by Lo et al,⁶ all had their glucocorticoid dose increased during pregnancy. The complications of pregnancy reported included pre-eclampsia requiring urgent Caesarean section, another patient had a Caesarean section due to arrest of descent. Hoepffner et al,⁵ on the other hand, did not change the prepregnancy regimes throughout all the 9 reported pregnancies. Ogilvie et al⁷ also did not adjust the glucocorticoid dose markedly, rather fludrocortisone dose was increased in the last trimester according to symptoms of postural hypotension reported by the patients.

The glucocorticoid to be used during pregnancy should be inactivated by placental 11-beta-hydroxysteroid dehydrogenase type II in order to minimise fetal adrenal suppression. Glucocorticoids with such property include hydrocortisone, cortisone acetate, prednisone, and methylprednisolone. Dexamethasone should be avoided as it can be transferred across the placenta to suppress the fetal adrenal gland. Regarding the mode of delivery, Caesarean section is recommended in view of previous operations of the genital tract.

In summary, we report an uneventful pregnancy in a Chinese woman with classical CAH giving birth to a healthy female infant with normal external genitalia. Our experience of managing the patient shows that with optimal control of the underlying disease process, child bearing is achievable in women with classical CAH.

References

1. Pang S, Shook MK. Current status of neonatal screening for congenital adrenal hyperplasia. *Curr Opin Pediatr* 1997;9:419-23.
2. Lee HH, Kuo JM, Chao HT, et al. Carrier Analysis and Prenatal Diagnosis of Congenital Adrenal Hyperplasia caused by 21-Hydroxylase Deficiency in Chinese. *J Clin Endocrinol Metab* 2000;85:597-600.
3. Mulaikal RM, Migeon CJ, Rock JA. Fertility rates in female patients with congenital adrenal hyperplasia due to 21 hydroxylase deficiency. *N Engl J Med* 1987;316:178-82.
4. Kuhnle U, Bullinger M, Schwarz HP. The quality of life in adult female patients with congenital adrenal hyperplasia: A comprehensive study of the impact of genital malformations and chronic disease on female patients life. *Eur J Pediatr* 1995;154: 708-16.

5. Hoepffner W, Schulze E, Bennek J, Keller E, Willgerodt H. Pregnancies in patients with congenital adrenal hyperplasia with complete or almost complete impairment of 21- hydroxylase activity. *Fertil Steril* 2004;81:1314-21.
6. Lo JC, Schwitzgebel VM, Tyrrell JB, et al. Normal Female Infants Born of Mothers with Classic Congenital Adrenal Hyperplasia due to 21-hydroxylase Deficiency. *J Clin Endocrinol Metab* 1999; 84:930-6.
7. Ogilvie CM, Crouch NS, Rumsby G, Creighton SM, Liao LM, Conway GS. Congenital adrenal hyperplasia in adults: a review of medical, surgical and psychological issues. *Clin Endocrinol* 2006;64:2-11.
8. Holmes-Walker DJ, Conway GS, Honour JW, Rumsby G, Jacobs HS. Menstrual disturbance and hypersecretion of progesterone in women with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. *Clin Endocrinol* 1995;43:291-6.
9. Berger NG, Repke JT, Woodruff JD. Markedly elevated serum testosterone in pregnancy without fetal virilization. *Obstet Gynecol* 1984;63:260-2.
10. Shozu M, Akasofu K, Harada T, Kubota Y. A new cause of female pseudohermaphroditism: Placental aromatase deficiency. *J Clin Endocrinol Metab* 1991;72:560-6.